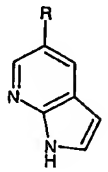
Claims

1. A compound of formula (I) as defined below:



(I)

wherein:

R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C_{1-12} alkyl, C_{2-12} alkenyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined below and wherein:

the C_{1-12} alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -$N(R^2)$-, -S(O)- and –$S(O_2)$- wherein each R^2 may be the same or different and is as defined below;

the C_{1-12} alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2_2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$; wherein each R^2 may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C_{1-12} alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, =NNHR^2, NNR^{2}R^2, =N-OR^2, =NNHCOR^2, =NNHCO$_2$R^2, =NNSO$_2$R^2, or =NR^2, wherein each R^2 may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R^3, COR^2, SO$_2$R^2 or CO$_2$R^2, wherein each R^2 and R^3 may be the same or different and is as defined below;

R^2 is hydrogen , C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO$_2$, CN, NR^{4}R^4, NR^{4}COR^4, NR^{4}CONR^{4}R^4, NR^{4}COR^4, NR^{4}CO$_2$R^4, CO$_2$R^4, COR^4, CONR$^4_2$, S(O)$_2$R^4, SONH$_2$, S(O)R^4, SO$_2$ NR^{4}R^4, NR^{4}S(O)$_2$R^4, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R^4)-, -S(O)- and –S(O$_2$)-, wherein each R^4 may be the same or different and is as defined below;

R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO$_2$, CN, NR^{4}R^4, NR^{4}COR^4, NR^{4}CONR^{4}R^4, NR^{4}COR^4, NR^{4}CO$_2$R^4, CO$_2$R^4, COR^4, CONR$^4_2$, S(O)$_2$R^4, SONH$_2$, S(O)R^4, SO$_2$ NR^{4}R^4, NR^{4}S(O)$_2$R^4, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R^4)-, -S(O)- and –S(O$_2$)-, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl; with the proviso that when R is phenyl substituted with branched C_6-alkyl (-CH(CH$_2$-CH(CH$_3$)(CH$_3$))-CH$_2$-) incorporating two insertions –(CO)-and-NH-, the C_6-alkyl group is not substituted with –CN;

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

2. A compound as claimed in claim 1, wherein R is an aryl or heteroaryl radical, optionally substituted with one or more of alkyl, haloalkyl, halogen,

OR^8, S R^8, SO R^8, $(NR^8)_2$, wherein R^8 is independently selected from hydrogen, C_{1-4} alkyl or haloalkyl.

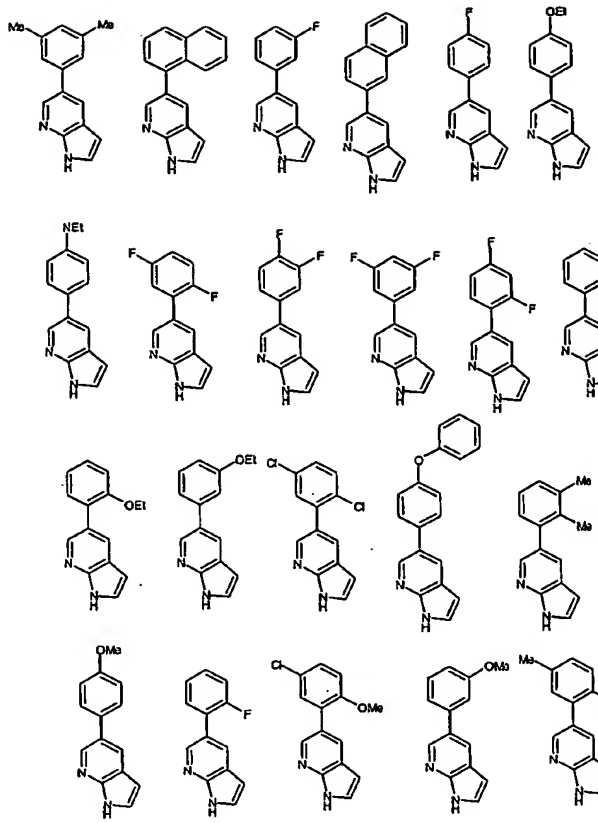
3. A compound as claimed in claim 1 wherein R is an optionally substituted aryl, preferably phenyl or napthyl.

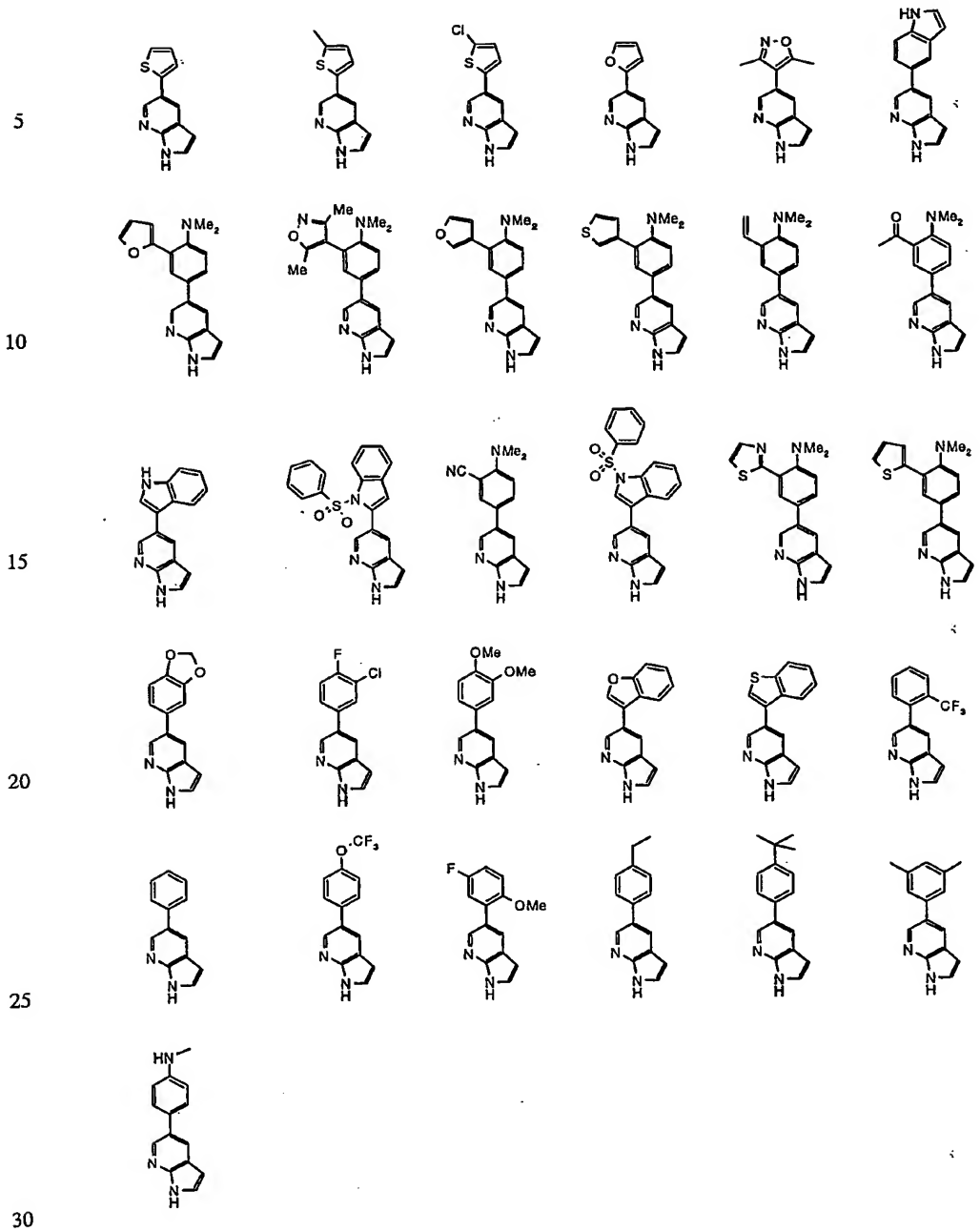
4. A compound as claimed in claim 3, wherein R is phenyl substituted in the 4-(para) position.

5. A compound as claimed in claim 3 or claim 4, wherein R is phenyl substituted by NR^6 R^6, where R^6 stands independently for H or C_{1-4} alkyl.

6. A compound as claimed in claim 3 or claim 4, wherein R is substituted aryl and the substituent is F, Cl or Br, preferably F; or haloalkyl, preferably CF_3, or alkyl, preferably methyl, ethyl or propyl.

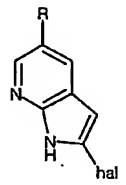
7. A compound as claimed in claim 1, which is one of the following:





8. A prodrug of a compound as defined in any of claims 1 to 7.

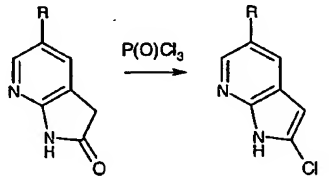
9. A process for the manufacture of any one or more of the compounds of any one of claims 1 to 7 which comprises hydrogenating a compound of the general formula (II):



(II)

in which R is as defined in claim 1 and hal stands for a halogen atom, e.g. using hydrogen and a catalyst such as Pd-C.

10. A process as claimed in claim 9, wherein the compound of the general formula (II) is made by halogenating a compound of the general formula (III) in the 2 position



(III) (II)

where R is as defined above and hal stands for halogen, e.g. using $P(O)Cl_3$ at elevated temperature (about 100°C).

11. A composition comprising a compound as defined in any of claims 1-7 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

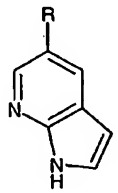
12. A composition as claimed in claim 11 further comprising one or more other active agent.

13. A composition as claimed in claim 11 wherein the composition further comprises an anti-inflammatory agent, for example a p38 inhibitor.

14. A process for the manufacture of a composition as defined in any of claims 11-13, comprising combining a compound as defined in any of claims 1-7, and any additional active agent, with the pharmaceutically acceptable carrier or diluent.

15. A compound as defined in any of claims 1-7, or a composition as defined in any of claims 11-13, for use in therapy.

16. A compound of formula (I)



(I)

or a composition comprising a compound of formula (I), for inhibiting JNK, wherein:

R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C_{1-12} alkyl, C_{2-12} alkenyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined below and wherein:

the C_{1-12} alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R^2)-, -S(O)-

and –$S(O_2)$- wherein each R^2 may be the same or different and is as defined below;

the C_{1-12} alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2{}_2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$; wherein each R^2 may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C_{1-12} alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, =$NNHR^2$, NNR^2R^2, =N-OR^2, =$NNHCOR^2$, =$NNHCO_2R^2$, =$NNSO_2R^2$, or =NR^2, wherein each R^2 may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R^3, COR^2, SO_2R^2 or CO_2R^2, wherein each R^2 and R^3 may be the same or different and is as defined below;

R^2 is hydrogen , C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4{}_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, SO_2 NR^4R^4, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -$N(R^4)$-, -S(O)- and –$S(O_2)$-, wherein each R^4 may be the same or different and is as defined below;

R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4{}_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, SO_2 NR^4R^4, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -$N(R^4)$-, -S(O)- and –$S(O_2)$-, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

17. A compound or a composition as defined in claim 16, for selectively inhibiting JNK3.

18. A compound or a composition as defined in claim 16, for use in the prevention or treatment of a JNK-mediated disorder.

19. A compound or a composition as claimed in claim 18, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or any condition associated with prostaglandin endoperoxidase synthase-2.

20. A compound or composition as claimed in claim 19, wherein the neurodegenerative disorder results from apoptosis and/or inflammation.

21. A compound or composition as claimed in claim 19 or claim 20, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

22. A compound or composition as claimed in claim 19 or 20, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

23. A compound or composition as claimed in claim 18, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glumerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytis anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

24. A method of treating or preventing a JNK-mediated disorder in an individual, which method comprises administering to said individual a compound or a composition as defined in claim 16.

25. A method as claimed in claim 24, wherein the individual is in need of the treatment or prevention of the disorder.

26. A method as claimed in claim 24 or 25, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder,

organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or any condition associated with prostaglandin endoperoxidase synthase-2.

27. A method as claimed in claim 26, wherein the neurodegenerative disorder results from apoptosis and/or inflammation.

28. A method as claimed in claim 26 or 27, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

29. A method as claimed in claim 26 or 27, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

30. A method as claimed in claim 24, 25 or 26, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glumerulonephritis,

scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytis anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

31. A method as claimed in any of claims 24-30, wherein one or more other active agent is administered to the individual simultaneously, subsequently or sequentially to administering the compound.

32. A method as claimed in claim 31, wherein the other active agent is an anti-inflammatory agent such as a p38 inhibitor.

33. Use of a compound as defined in claim 16 in the manufacture of a medicament for the prevention or treatment of a JNK-mediated disorder.

34. Use as claimed in claim 33, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or any condition associated with prostaglandin endoperoxidase synthase-2.

35. Use as claimed in claim 34, wherein the neurodegenerative disorder results from apoptosis and/or inflammation.

36. Use as claimed in claim 34 or 35, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia;

dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

37. Use as claimed in claim 34 or 35, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

38. Use as claimed in claim 34, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glumerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytis anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

39. Use as claimed in any of claims 33-38, wherein the medicament further includes one or more other active agent.

40. Use as claimed in claim 39, wherein the other active agent is an anti-inflammatory agent such as a p38 inhibitor.

41. An assay for determining the activity of the compounds as defined in any of claims 1-7, comprising providing a system for assaying the activity and assaying the activity of a compound as defined in any of claims 1-7.

42. An assay as claimed in claim 41, wherein the assay is for the JNK inhibiting activity of the compound, preferably for the JNK3-specific inhibiting activity of the compound.

43. An assay as claimed in claim 41 or 42, wherein the assay is a Scintillation Proximity Assay (SPA) using radiolabelled ATP, or is ELISA.

44. A method of inhibiting the activity or function of a JNK, particularly JNK3, which method comprises exposing a JNK to a compound or composition as defined in claim 16.

45. A method as claimed in claim 44, which is performed in a research model.

46. A method as claimed in claim 45, wherein the research model is an animal model.